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☐ 1. Document ID: US 20040052833 A1

L3: Entry 1 of 21 File: PGPB Mar 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040052833
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040052833 A1

TITLE: Sodium dodecyl sulfate compositions for inactivating prions

PUBLICATION-DATE: March 18, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Prusiner, Stanley B.	San Francisco	CA	US	
Supattapone, Surachai	Hanover	NH	US	

US-CL-CURRENT: 424/442; 530/350

ABSTRACT:

An antiseptic composition useful in destroying the infectivity of infectious proteins such as prions is disclosed. The antiseptic composition is preferably maintained at either a low pH of 4.0 or less or a high pH of 10.0 or more either of which allows for an environment under which the active component (which is preferably sodium dodecyl sulfate) destroys infectivity. The composition may be added to blood, blood products, collagen, tissues and organs prior to transplantation. The composition also may be added to livestock feed to denature any prions in the livestock. Methods of denaturing infectious proteins are also disclosed which method can use but do not require higher temperatures and long period of exposure.

L3: Entry 1 of 21 File: PGPB Mar 18, 2004

DOCUMENT-IDENTIFIER: US 20040052833 A1
TITLE: Sodium dodecyl sulfate compositions for inactivating prions

Detail Description Paragraph:
[0244] Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested

increases .alpha.-helical content, suggesting that such conditions might dissociate PrP into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 20030104358 A1

L3: Entry 2 of 21 File: PGPB Jun 5, 2003

PGPUB-DOCUMENT-NUMBER: 20030104358
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030104358 A1

TITLE: Diagnosis methods based on microcompetition for a limiting GABP complex

PUBLICATION-DATE: June 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Polansky, Hanan	Rochester	NY	US	

US-CL-CURRENT: 435/5; 435/6

ABSTRACT:

Microcompetition for GABP between a foreign polynucleotide and cellular GABP regulated genes is a risk factor associated with many chronic diseases such as obesity, cancer, atherosclerosis, stroke, osteoarthritis, diabetes, asthma, and other autoimmune diseases. The invention uses this novel discovery to present assays for the diagnosis of these chronic diseases. The assays are based on measuring the cellular copy number of the foreign polynucleotide, measuring the rate of complex formation between GABP and either the foreign polynucleotide, or a cellular GABP regulated gene, identifying modified expression of a cellular GABP regulated gene, or identifying modified activity of the gene product of a GABP regulated gene. The invention also presents other foreign polynucleotide-type assays.

L3: Entry 2 of 21 File: PGPB Jun 5, 2003

Detail Description Table CWU:
High-throughput methods for detection of genetic variation. Biotechniques 2001 Feb; 30(2): 318-22, 324, 326 passim. .sup.158 Tawata M, Aida K, Onaya T. Screening for genetic mutations. A review. Comb Chem High Throughput Screen. 2000 Feb; 3(1): 1-9. Review. .sup.159 Pecheniuk N M, Walsh T P, Marsh N A. DNA technology for the detection of common genetic variants that predispose to thrombophilia. Blood Coagul Fibrinolysis 2000 Dec; 11(8): 683-700. .sup.160 Cotton R G. Current methods of mutation detection. Mutat Res. 1993 Jan; 285(1): 125-44. Review. .sup.161 Prosser J. Detecting single-base mutations. Trends Biotechnol. 1993 Jun; 11(6): 238-46. Review. .sup.162 Abrams E S, Murdaugh S E, Lerman L S. Comprehensive detection of single base changes in human genomic DNA using denaturing gradient gel electrophoresis and a GC clamp. Genomics. 1990 Aug; 7(4): 463-75. .sup.163 Forrest S, Cotton R G. Methods of detection of single base substitutions in clinical genetic practice. Mol Biol Med. 1990 Oct; 7(5): 451-9. Review. .sup.164 Graham C A, Hill A J. Introduction to DNA sequencing. Methods Mol Biol. 2001; 167: 1-12. Review. .sup.165 Rapley R. eds. PCR sequencing protocols. Humana Press, Totowa, NJ, 1996. .sup.166 Marziali A, Akeson M. New DNA sequencing methods. Annu Rev Biomed Eng 2001; 3: 195-223. .sup.167 Dovichi N J, Zhang J. DNA sequencing by capillary array electrophoresis. Methods Mol Biol. 2001; 167: 225-39. Review. .sup.168 Huang G M. High-throughput DNA sequencing: a genomic data manufacturing process. DNA Seq. 1999; 10(3): 149-53. Review. .sup.169 Schmalzing D, Koutny L, Salas-Solano O, Adourian A, Matsudaira P, Ehrlich D. Recent developments in DNA sequencing by capillary and microdevice electrophoresis. Electrophoresis. 1999 Oct; 20(15- 16): 3066-77. Review. .sup.170 Murray K K. DNA sequencing by mass spectrometry. J Mass Spectrom. 1996 Nov; 31(11): 1203-15. .sup.171 Cohen A S, Smisek D L, Wang B H. Emerging technologies for sequencing antisense oligonucleotides: capillary electrophoresis and mass spectrometry. Adv Chromatogr. 1996; 36: 127-62. Review. .sup.172 Griffin H G, Griffin A M. DNA sequencing. Recent innovations and future trends. Appl Biochem Biotechnol. 1993 Jan-Feb; 38(1-2): 147-59. Review. .sup.173 Watts D, MacBeath J R. Automated fluorescent DNA sequencing on the ABI PRISM 310 Genetic Analyzer. Methods Mol Biol. 2001; 167: 153-70. Review. .sup.174 MacBeath J R, Harvey S S, Oldroyd N J. Automated fluorescent DNA sequencing on the ABI PRISM 377. Methods Mol Biol. 2001; 167: 119-52. Review. .sup.175 Smith L M, Brumley R L Jr, Buxton E C, Giddings M, Marchbanks M, Tong X. High-speed automated DNA sequencing in ultrathin slab gels. Methods Enzymol. 1996; 271: 219-37. Review. .sup.176 Maxam A M, Gilbert W. A new method for sequencing DNA. Proc Natl Acad Sci USA. 1977 Feb; 74(2): 560-4. .sup.177 Saleeba J A, Cotton R G. Chemical cleavage of mismatch to detect mutations. Methods Enzymol. 1993; 217: 286-95. .sup.178 Takahashi N, Hiyama K, Kodaira M, Satoh C. An improved method for the detection of genetic variations in DNA with denaturing gradient gel electrophoresis. Mutat Res. 1990 Apr; 234(2): 61-70. .sup.179 Cotton R G, Rodrigues N R, Campbell R D. Reactivity of cytosine and thymine in single-base-pair mismatches with hydroxylamine and osmium tetroxide and its application to the study of mutations. Proc Natl Acad Sci USA. 1988 Jun; 85(12): 4397-401. .sup.180 Myers R M, Latin Z, Maniatis T. Detection of single base substitutions by ribonuclease cleavage at mismatches in RNA:DNA duplexes. Science. 1985 Dec 13; 230(4731): 1242-6. .sup.181 Myers R M, Lumelsky N, Lerman L S, Maniatis T. Detection of single base substitutions in total genomic DNA. Nature. 1985 Feb 7-13; 313(6002): 495-8. .sup.182 Xu J F, Yang Q P, Chen J Y, van Baalen M R, Hsu I C. Determining the site and nature of DNA mutations with the cloned MutY mismatch repair enzyme. Carcinogenesis. 1996 Feb; 17(2): 321-6. .sup.183 Hsu I C, Yang Q, Kahng M W, Xu J F. Detection of DNA point mutations with DNA mismatch repair enzymes. Carcinogenesis. 1994 Aug; 15(8): 1657-62. .sup.184 Miterski B, Kruger R, Wintermeyer P, Epplen J T. PCR/SSCP detects reliably and efficiently DNA sequence

(3): 73- 9. Review. .sup.187 Lipshutz R J, Morris D, Chee M, Hubbell E, Kozal M J, Shah N, Shen N, Yang R, Fodor S P. Using oligonucleotide probe arrays to access genetic diversity. Biotechniques 1995 Sep; 19(3): 442-7. .sup.188 Guo Z, Guilfoyle R A, Thiel A J, Wang R, Smith L M. Direct fluorescence analysis of genetic polymorphisms by hybridization with oligonucleotide arrays on glass supports. Nucleic Acids Res 1994 Dec 11; 22(24): 5456-65. .sup.189 Saiki R K, Walsh P S, Levenson C H, Erlich H A. Genetic analysis of amplified DNA with immobilized sequence-specific oligonucleotide probes. Proc Natl Acad Sci USA. 1989 Aug; 86(16): 6230-4. .sup.190 Efremov D G, Dimovski A J, Jankovic L, Efremov G D. Mutant oligonucleotide extension amplification: a nonlabeling polymerase-chain-reaction-based assay for the detection of point mutations. Acta Haematol 1991; 85(2): 66-70. .sup.191 Gibbs R A, Nguyen P N, Caskey C T. Detection of single DNA base differences by competitive oligonucleotide priming. Nucleic Acids Res. 1989 Apr 11; 17(7): 2437-48. .sup.192 Geisler J P, Hatterman-Zogg M A, Rathe J A, Lallas T A, Kirby P, Buller R E. Ovarian cancer BRCA1 mutation detection: Protein truncation test (PTT) outperforms single strand conformation polymorphism analysis (SSCP). Hum Mutat. 2001 Oct; 18(4): 337-44. .sup.193 Moore W, Bogdarina I, Patel UA, Perry M, Crane-Robinson C. Mutation detection in the breast cancer gene BRCA1 using the protein truncation test. Mol Biotechnol. 2000 Feb; 14(2): 89-97. .sup.194 van der Luijt R, Khan P M, Vasen H, van Leeuwen C, Tops C, Roest P, den Dunnen J, Fodde R. Rapid detection of translation-terminating mutations at the adenomatous polyposis coli (APC) gene by direct protein truncation test. Genomics. 1994 Mar 1; 20(1): 1-4. .sup.195 Roest P A, Roberts R G, Sugino S, van Ommen G J, den Dunnen J T. Protein truncation test (PTT) for rapid detection of translation-terminating mutations. Hum Mol Genet. 1993 Oct; 2(10): 1719-21. .sup.196 Burnett W N. Western blotting electrophoretic transfer of proteins from SDS-polyacrylamide to unmodified nitrocellulose and autoradiographic detection with antibody and radioiodinated protein A. Ann Biochem, 112: 195-203 1981. .sup.197 Virts E L, Raschke W C. The Role of Intron Sequences in High Level Expression from CD45 cDNA Constructs. J Biol Chem, 276, 19913-19920, 2001. .sup.198 Chen C, Okayama H. Calcium phosphate-mediated gene transfer: A highly efficient system for stably transforming cells with plasmid DNA. BioTech. 6, 632-638, 1988. .sup.199 Lopata M A, Cleveland D W, Sollner-Webb B. High-level expression of a chloramphenicol acetyltransferase gene by DEAE-dextran-mediated DNA transfection coupled with a dimethyl sulfoxide or glycerol shock treatment. Nucl. Acids Res. 12, 5707-5717, 1984. .sup.200 Gorman C M, Moffat L F, Howard B H. Recombinant genomes which express chloramphenicol acetyltransferase in mammalian cells. Mol. Cell. Biol. 2, 1044-1051, 1982. .sup.201 Luo R Z, Peng H, Xu F, Bao J, Pang Y, Pershad R, Issa J J, Liao W S, Bast R C, Yu Y. Genomic structure and promoter characterization of an imprinted tumor suppressor gene ARHI(1). Biochim Biophys Acta, 1519, 216-222, 2001. .sup.202 Sowa Y, Shiio Y, Fujita T, Matsumoto T, Okuyama Y, Kato D, Inoue J, Sawada J, Goto M, Watanabe H, Handa H, Sakai T. Retinoblastoma binding factor 1 site in the core promoter region of the human RB gene is activated by hGABP/E4TF1. Cancer Res. 57, 3145-3148, 1997. .sup.203 Sucharov C, Basu A, Carter R S, Avadhani N G. A novel transcriptional initiator activity of the GABP factor binding ets sequence repeat from the murine cytochrome c oxidase Vb gene. Gene Expr. 5, 93-111, 1995. .sup.204 Ouyang L, Jacob K K, Stanley F M. GABP mediates insulin-increased prolactin gene transcription. J. Biol. Chem. 271, 10425-10428, 1996. .sup.205 Staskus K A, Embretson J E, Retzel E F, Beneke J, Haase A T. PCR in situ: new technologies with single cell resolution for the detection and investigation of viral latency and persistence. http://www.cbc.umn.edu/VirtLibrary/- Staskus/chap-shoot2.fm.html, 1994. .sup.206 Schuurhuis G J, Muijen M M, Oberink J W, de Boer F, Ossenkoppele G J, Broxterman H J. Large populations of non-clonogenic early apoptotic CD34-positive cells are present in frozen-thawed peripheral blood stem cell transplants. Bone Marrow

Between a Metallothionein Regulatory Element and the SV40 Enhancer. Science 1986 232: 76-80. .sup.210 Adam G I, Miller S J, Ulleras E, Franklin G C. Cell-type-specific modulation of PDGF-B regulatory elements via viral enhancer competition: a caveat for the use of reference plasmids in transient transfection assays. Gene. 1996 Oct 31; 178(1-2): 25-9. .sup.211 Allebach E S, Boettiger D, Pacifici M, Adams S L. Control of types I and II collagen and fibronectin gene expression in chondrocytes delineated by viral transformation. Mol Cell Biol. 1985 May; 5(5): 1002-8. .sup.212 Parker I M, Smith A A, Gevers W. Absence of .alpha.2(1) Procollagen Synthesis in a Clone of SV40- transformed WI-38 Human Fibroblasts. The Journal of Biological Chemistry, 1989, 264(13): 7147-7152.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 3. Document ID: US 20030009291 A1

L3: Entry 3 of 21 File: PGPB Jan 9, 2003

PGPUB-DOCUMENT-NUMBER: 20030009291
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030009291 A1

TITLE: Structural prediction of allosterism

PUBLICATION-DATE: January 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Freire, Ernesto	Baltimore	MD	US	

US-CL-CURRENT: 702/19

ABSTRACT:

The present invention provides a computer-assisted method for creating and displaying a model of a molecule in which residues that are affected by the binding of a ligand to the molecule are highlighted, making it possible to trace the path of propagation of a binding signal through the molecule. In order to carry out the method, the binding site determinants of the molecule are determined and the binding constant for the ligand is calculated. The states of a conformational ensemble that are binding competent are identified, and the Gibbs energy and probability of each state and the stability constant per residue of the molecule are calculated in the presence and absence of the ligand. Those residues that display a difference in stability constant in the presence vs absence of ligand are those which are affected by the binding of the ligand.

L3: Entry 3 of 21 File: PGPB Jan 9, 2003

DOCUMENT-IDENTIFIER: US 20030009291 A1

the binding site for ligand X is formed. This necessitates the identification of the residues involved in binding (the binding site determinants) and the selection of those states in the ensemble in which those residues are in a binding competent conformation. Further, both Ka,.sub.0 and Ka,i must be determined, either computationally or by experimental means. Identification of the binding site determinants is accomplished by utilizing high resolution structures of the free protein, the free ligand, and the protein-ligand complex. The contribution of each individual residue to the Gibbs energy of binding is calculated by applying a parameterized Gibbs energy function (e.g. equation 4) to the high resolution structures. Each thermodynamic quantity, .DELTA.Y, that contributes to the Gibbs energy (where .DELTA.Y refers to .DELTA.ASA, .DELTA.H, .DELTA.S, .DELTA.G, etc. as listed in equation 4) is evaluated at the residue level as:

Detail Description Paragraph:
[0038] Identification of the binding determinants in this manner allows the identification of those states which are binding competent: protein conformational states of the ensemble are considered to be binding competent if the residues that constitute the binding determinants are in the native (template or folded) conformation in those states. The Gibbs energy of each binding competent state is modified by equation 6 by setting [X] equal to a given concentration of ligand. While any concentration can be used in the calculation, in a preferred embodiment the concentration is the one that elicits 99% saturation. This concentration is given by [X]=100/K.sub.1,0. Note that, if no ligand is present, then [X]=0 and Equation 6 becomes equivalent to Equation 4.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 4. Document ID: US 20030004312 A1

L3: Entry 4 of 21 File: PGPB Jan 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030004312
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030004312 A1

TITLE: Sodium dodecyl sulfate compositions for inactivating prions

PUBLICATION-DATE: January 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Prusiner, Stanley B.	San Francisco	CA	US	
Supattapone, Surachai	Hanover	NH	US	

US-CL-CURRENT: 530/350

ABSTRACT:

An antiseptic composition useful in destroying the infectivity of infectious

transplantation. The composition also may be added to livestock feed to denature any prions in the livestock. Methods of denaturing infectious proteins are also disclosed which method can use but do not require higher temperatures and long period of exposure.

L3: Entry 4 of 21 File: PGPB Jan 2, 2003

DOCUMENT-IDENTIFIER: US 20030004312 A1
TITLE: Sodium dodecyl sulfate compositions for inactivating prions

Detail Description Paragraph:
[0243] Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible: (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions; (2) Treatment of PrP 27-30 with acid decreases turbidity and increases .alpha.-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 5. Document ID: US 20020045192 A1

L3: Entry 5 of 21 File: PGPB Apr 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020045192
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020045192 A1

TITLE: Arf and HDM2 interaction domains and methods of use thereof

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

US-CL-CURRENT: 435/7.1; 514/1, 702/19

ABSTRACT:

The present invention discloses that the binding of Arf with Dm2 results in specific domains of both proteins undergoing a dramatic transition from disordered conformations to extended structures comprised of .beta.-strands. The presence of these specific domains is necessary and sufficient for the formation of the highly stable extended .beta. structures formed between these two proteins. The present invention further exploits this discovery by providing unique methods for identifying and/or designing compounds that mimic, inhibit and/or enhance the effect of Arf on Dm2. The present invention also provides specific protein fragments derived from Arf and Dm2 that play a critical role in the binding of these two important regulatory proteins.

DOCUMENT-IDENTIFIER: US 20020045192 A1
TITLE: Arf and HDM2 interaction domains and methods of use thereof

Detail Description Paragraph:
[0172] The importance of dynamically disordered proteins or domains in biological systems, and in the regulation of cell division, is well established [Kriwacki et al., Proc. Natl. Acad. Sci. USA, 93:11504-11509 (1996); Uversky et al., Protein Sci., 8:161-73 (1999); Sosnick et al., Proteins, 24:427-32 (1996); Dyson et al., Biol., 5:499-503 (1998); Plaxco et al., Nature, 386:657-658 (1997); Wright et al., J. Mol Biol, 293:321-31 (1999)]. For example, the N-terminal domains of the cyclin dependent kinase inhibitors p21 [Kriwacki et al., Proc. Natl. Acad. Sci. USA, 93:11504-11509 (1996); Kriwacki et al., J. Amer. Chem. Soc., 118:5320-5321 (1996)] and p27 are largely unstructured prior to binding of their cellular targets. Currently, the functional advantage(s) of the `folding-on-binding` mechanism is not well understood. Intuitively, the loss of conformational entropy associated with folding will reduce the Gibbs free energy of binding for dynamically disordered proteins binding their targets [Kriwacki et al., Proc. Natl. Acad. Sci. USA, 93:11504-11509 (1996); Spolar et al., Science, 263:777-84 (1994)]. It has been suggested that the advantage of this mechanism is to enhance specificity [Spolar et al., Science, 263:777-84 (1994)] and/or to allow multiple, structurally distinct substrates to be bound [Kriwacki et al., Proc. Natl. Acad. Sci. USA, 93:11504-11509 (1996); Kim et al., Nature, 404:151-8 (2000)]. A recent computational study focused on understanding the impact of conformational entropy in protein folding [Pappu et al., Proc Natl Acad Sci USA, 97:12565-70 (2000)] suggests that the entropy penalty may not be as great as commonly envisioned due to steric restrictions by amino acid side chains on the vastness of polypeptide conformational space. While dynamic and highly disordered, flexible polypeptides are probably conformationally restrained in solution by steric and other interaction forces; the challenges for the future are to develop approaches to quantitatively describe these biased conformations and to relate them to biological function. The need for such studies continues to grow as more examples of biologically active, dynamically disordered proteins appear in the literature. The significance of the observations disclosed herein with the Arf:Hdm2 system is that, in contrast to previous observations of the folding-on-binding phenomenon involving a single disordered protein, both components of the

PGPUB-DOCUMENT-NUMBER: 20020041862
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020041862 A1

TITLE: Method of sterilizing

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Prusiner, Stanley B.	San Francisco	CA	US	
Supattapone, Surachai	San Francisco	CA	US	
Scott, Michael R.	San Francisco	CA	US	

US-CL-CURRENT: 424/78.27; 422/28

ABSTRACT:

A method of sterilizing objects as well as the sterilized objects obtained from the method are disclosed. The method involves contacting an object such as a medical device to be reused with polycationic dendrimer under conditions which result in rendering a conformationally altered protein (e.g. a prion) non-infectious. A disinfecting agent or surgical scrub composition which comprises the dendrimers is also disclosed as are gelatin capsules treated with polycationic dendrimers.

L3: Entry 6 of 21 File: PGPB Apr 11, 2002

DOCUMENT-IDENTIFIER: US 20020041862 A1
TITLE: Method of sterilizing

Detail Description Paragraph:
[0121] Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible. (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions. (2) Treatment of PrP 27-30 with acid decreases turbidity and increases a-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic

endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

☐ 7. Document ID: US 20020041859 A1

L3: Entry 7 of 21 File: PGPB Apr 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020041859
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020041859 A1

TITLE: Antiseptic compositions for inactivating prions

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Prusiner, Stanley B.	San Francisco	CA	US	
Supattapone, Surachai	Hanover	NH	US	

US-CL-CURRENT: 424/70.24; 424/405, 424/451, 424/709

ABSTRACT:

An antiseptic composition useful in destroying the infectivity of infectious proteins such as prions is disclosed. The antiseptic composition is preferably maintained at a pH of 4.0 or less which allows for an environment under which the active component destroys infectivity. The composition may be added to blood, blood products, collagen, tissues and organs prior to transplantation. The composition also may be added to livestock feed to denature any prions in the livestock. Methods of denaturing infectious proteins are also disclosed.

L3: Entry 7 of 21 File: PGPB Apr 11, 2002

DOCUMENT-IDENTIFIER: US 20020041859 A1
TITLE: Antiseptic compositions for inactivating prions

Detail Description Paragraph:
[0230] Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc . The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible: (1)

aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrPS.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 8. Document ID: US 20010051374 A1

L3: Entry 8 of 21 File: PGPB Dec 13, 2001

PGPUB-DOCUMENT-NUMBER: 20010051374
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010051374 A1

TITLE: HIGH EFFICIENCY GENETIC MODIFICATION METHODS

PUBLICATION-DATE: December 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
MCLAUGHLIN-TAYLOR, ELIZABETH	SAN CLEMENTE	CA	US	
KRUGER, MARK	ENCINITAS	CA	US	
LUNDAK, CHERYL	SAN DIEGO	CA	US	
KILLION, CATHERINE	LONG BEACH	CA	US	

US-CL-CURRENT: 435/455; 435/320.1, 435/372.3, 435/456

ABSTRACT:

A method is provided for producing a population of genetically modified T cells. In the method, an in vitro population of T cells is activated by contacting said population with a CD3 binding agent. Genetic modification is then carried out with the activated T cells by contacting the same with a suitable gene transfer vector.

L3: Entry 8 of 21 File: PGPB Dec 13, 2001

DOCUMENT-IDENTIFIER: US 20010051374 A1
TITLE: HIGH EFFICIENCY GENETIC MODIFICATION METHODS

Detail Description Paragraph:

cell surface-bound cofactor, thrombomodulin. Upon binding to this protein, thrombin undergoes a conformational change that greatly reduces it's ability to perform the procoagulant reactions mentioned above, while greatly increasing the rate of activation of protein C zymogen, thus changing specificity from a procoagulant to an anticoagulant enzyme. In accordance with this model, infusion of low levels of thrombin has been shown to be antithrombotic (Gruber (1990) Circ. 82:578, Hanson (1993) J. Clin. Invest. 92:2003, McBane (1995) Thromb. Haemostas. 74:879). Thrombin variants with similar changes in specificity in the absence of thrombomodulin have been developed (Dang (1997) Nature Biotech. 15:146, Gibbs (1995) Nature 378:413, (1991) Proc. Natl. Acad. Sci. USA 88:7371, Wu (1991) Proc. Natl. Acad. Sci. USA 88:6775, and Guinto (1995) Proc. Natl. Acad. Sci. USA 92:11185). Delivery of these variants by the means of gene transfer vectors and the methods of genetic modification described herein is thus useful in reducing thrombosis in individuals at risk thereof.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 9. Document ID: US 20010000807 A1

L3: Entry 9 of 21 File: PGPB May 3, 2001

PGPUB-DOCUMENT-NUMBER: 20010000807
PGPUB-FILING-TYPE: new-utility
DOCUMENT-IDENTIFIER: US 20010000807 A1

TITLE: Method for prediction of binding targets and the design of ligands

PUBLICATION-DATE: May 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Freire, Ernesto	Baltimore	MD	US	
Luque, Irene	Baltimore	MD	US	

US-CL-CURRENT: 703/12; 703/11

ABSTRACT:

A computer-based method for the identification of binding targets in proteins and other macromolecules. More particularly, the invention includes an algorithm aimed at predicting binding targets in proteins. This algorithm, named Woolford, requires knowledge of the high resolution structure of the protein but no knowledge of the location or identity of natural binding sites or ligands. Binding targets in the protein are identified and classified according to their expected optimal affinities. Binding targets can be located at the protein surface or at internal surfaces that become exposed as a result of partial unfolding, conformational changes, subunit dissociation, or other events. The entire protein is mapped according to the binding potential of its constituent atoms. Once binding targets are identified, optimal ligands are designed and progressively built by the

selected target, and 4) refinement of lead compounds by defining the location and nature of chemical groups for optimal binding affinity.

DOCUMENT-IDENTIFIER: US 20010000807 A1

TITLE: Method for prediction of binding targets and the design of ligands

Detail Description Paragraph:

71. The Gibbs energy of binding is composed of enthalpic and entropic components. Both components include contributions due to the formation of interactions between ligand and protein, and contributions due to changes in hydration. The enthalpic contributions are a function of the separation distance between atoms and the changes in atomic accessibility to the solvent. The entropy change contain solvent contributions which are also proportional to changes in solvent accessibility, and the reduction in conformational degrees of freedom. Changes in translational degrees of freedom are the same for different ligands and therefore do not contribute to discrimination between binding affinities even though they contribute to the actual affinity.

Detail Description Paragraph:

88. In the above situation, the total Gibbs energy associated with the binding of the ligand is the sum of the Gibbs energy required to unfold the region of the protein that exposes the binding site (or the Gibbs energy for the conformation change) plus the intrinsic Gibbs energy of binding.

Detail Description Paragraph:

119. The Gibbs energy of binding is composed of enthalpic and entropic components. Both components include contributions due to the formation of interactions between ligand and protein, and contributions due to changes in hydration. The enthalpic contributions are a function of the separation distance between atoms and the changes in atomic accessibility to the solvent. The entropy change contains solvent contributions which are also proportional to changes in solvent accessibility, and the reduction in conformational degrees of freedom. Electrostatic interactions and protonation/deprotonation events coupled to binding are also important and are included in the analysis. Changes in translational degrees of freedom are the same for different ligands and therefore do not contribute to discriminate between binding affinities even though they contribute to the actual affinity.

Detail Description Paragraph:

128. In all cases presented here the Gibbs energy of binding, .DELTA.G, was calculated from the published crystallographic structures using procedures previously described (D'Aquino et al., 1996; Gomez et al., 1995(a); Gomez et al., 1995(b); Hilser et al., 1996(b); Luque et al., 1996). These calculations require the structures of the complex as well as the structures of the unligated protein and unligated inhibitor. In this approach, the generic portion of the Gibbs energy, .DELTA.G.sub.gen, is calculated from a separate computation of its enthalpy and entropy components. This portion of the Gibbs energy contains those contributions typically associated with the formation of secondary and tertiary structure (van der Waals interactions, hydrogen bonding, hydration and conformational entropy). Additional contributions to the Gibbs energy of binding are not separated into enthalpic and entropic components. They include electrostatic and ionization effects, Gion, and the contribution of the change in translational degrees of

complexes for which the structure of the free enzyme is available the calculations were performed by using both, the structure of the free enzyme (Spinelli et al., 1991), as well as the structure of the enzyme in the complex but without the inhibitor, as the unligated protein. The results were equivalent in both cases, the differences in Gibbs energies being smaller than 0.5 kcal/mole on the average. For those cases in which deviations were larger (pdb files 2upj, 1hvi, 1hvj, 1hvk, 9hvp) the deviations were traced to the side chain conformations of Phe 53B, Lys 55B, Arg 41A and Arg 41B. These side chains are solvent exposed and far away from the binding site, indicating that the conformational differences are not related to the inhibitor. The statistical analysis of the data reveals that the free energies of binding are predicted with a standard deviation of .+-.1.1 kcal/mol and a standard error of 0.3 kcal/mol. The standard deviation amounts to a relative uncertainty of .+-.10%. The correlation analysis between the experimental and predicted .DELTA.G values yields a slope of 0.982 with a correlation coefficient of 0.85. The structural predictions show no systematic deviations and are accurate enough to permit an examination of the different contributions to the binding energetics.

Detail Description Paragraph:
188. Once the mutation is made it is necessary to sample the ensemble of possible conformations and evaluate the energy and corresponding probability of each conformation. The probability of a single peptide conformation, defined by a specific set of side chain and backbone coordinates, is dictated by a Gibbs energy function, .DELTA.G.sub.ef, specified by the enthalpy of intra and intermolecular peptide/protein interactions plus the enthalpy and entropy of solvation. .DELTA.G.sub.ef is a function of the side chain and backbone torsional angles. By definition, the conformational entropy of the peptide itself does not enter into the equation. .DELTA.G.sub.ef is the Gibbs energy function or Gibbs potential function of a single conformation and should not be confused with the Gibbs energy of binding which includes all permissible conformations. The situation is illustrated in FIGS. 15A and 15B for two hypothetical conformations of a side chain. These conformations exhibit not only different intramolecular interactions but also different degrees of solvation that define the Gibbs energy function, .DELTA.G.sub.ef. The probability of any given conformation is given by the equation 4 P i = - G ef , i / R T j - G efj / R T

Detail Description Paragraph:
197. The binding affinity of the peptide for the protein is dictated by the Gibbs energy of binding which is calculated from the structures of the complex, the free protein and the free peptide as described before (Bardi et al., 1997; D'Aquino et al., 1996; Gomez et al., 1995(a); Gomez et al., 1995(b); Hilser et al., 1996(b); Luque et al., 1996). For each mutant complex the atomic coordinates corresponding to the conformation that minimizes the Gibbs potential function were used. For the free peptides the solvent accessibilities correspond to a Boltzmann weighted average of side chain and backbone conformations (Luque et al., 1996).

Detail Description Paragraph:
202. For endothiapepsin, the high resolution structures of the protein in its free and bound forms are known, and accurate calculations of binding affinities are possible. In many cases, however, only the structure of the complex is known. If this is the case, the binding Gibbs energies of the mutants relative to the wild type can still be calculated with the same accuracy, and therefore peptide design can be done with the same precision. This situation holds even if there is a significant conformational change between the free and complexed proteins.

type pepstatin A. The difference in binding Gibbs energies is mainly entropic and due primarily to the loss of conformational entropy of the glutamate upon binding. This loss of conformational entropy is not compensated by a favorable interaction either enthalpic or entropic, and results in a significant increase in .DELTA.G and consequent loss of binding affinity. FIG. 20 shows the predicted location of the glutamate residue.

☐ 10. Document ID: US 6720355 B2

L3: Entry 10 of 21 File: USPT Apr 13, 2004

US-PAT-NO: 6720355
DOCUMENT-IDENTIFIER: US 6720355 B2

TITLE: Sodium dodecyl sulfate compositions for inactivating prions

DATE-ISSUED: April 13, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Prusiner; Stanley B.	San Francisco	CA		
Supattapone; Surachai	Hanover	NH		

US-CL-CURRENT: 514/557; 424/405, 426/335, 426/532, 514/558

ABSTRACT:

An antiseptic composition useful in destroying the infectivity of infectious proteins such as prions is disclosed. The antiseptic composition is preferably maintained at either a low pH of 4.0 or less or a high pH of 10.0 or more either of which allows for an environment under which the active component (which is preferably sodium dodecyl sulfate) destroys infectivity. The composition may be added to blood, blood products, collagen, tissues and organs prior to transplantation. The composition also may be added to livestock feed to denature any prions in the livestock. Methods of denaturing infectious proteins are also disclosed which method can use but do not require higher temperatures and long period of exposure.

1 Claims, 26 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 12

L3: Entry 10 of 21 File: USPT Apr 13, 2004

DOCUMENT-IDENTIFIER: US 6720355 B2
TITLE: Sodium dodecyl sulfate compositions for inactivating prions

that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible: (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions; (2) Treatment of PrP 27-30 with acid decreases turbidity and increases .alpha.-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

☐ 11. Document ID: US 6719988 B2

L3: Entry 11 of 21 File: USPT Apr 13, 2004

US-PAT-NO: 6719988
DOCUMENT-IDENTIFIER: US 6719988 B2

TITLE: Antiseptic compositions for inactivating prions

DATE-ISSUED: April 13, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Prusiner; Stanley B.	San Francisco	CA		
Supattapone; Surachai	Hanover	NH		

US-CL-CURRENT: 424/405; 424/406, 424/78.07, 424/93.1, 424/93.6, 514/553, 514/557, 514/578, 514/709

ABSTRACT:

An antiseptic composition useful in destroying the infectivity of infectious proteins such as prions is disclosed. The antiseptic composition is preferably maintained at a pH of 4.0 or less which allows for an environment under which the active component destroys infectivity. The composition may be added to blood, blood products, collagen, tissues and organs prior to transplantation. The composition also may be added to livestock feed to denature any prions in the livestock.

DOCUMENT-IDENTIFIER: US 6719988 B2
TITLE: Antiseptic compositions for inactivating prions

Detailed Description Text (220):
Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible: (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions; (2) Treatment of PrP 27-30 with acid decreases turbidity and increases .alpha.-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrPS.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw De

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☐ 12. Document ID: US 6517855 B2

L3: Entry 12 of 21 File: USPT Feb 11, 2003

US-PAT-NO: 6517855
DOCUMENT-IDENTIFIER: US 6517855 B2

TITLE: Method of sterilizing

DATE-ISSUED: February 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Prusiner; Stanley B.	San Francisco	CA		
Supattapone; Surachai	San Francisco	CA		
Scott; Michael R.	San Francisco	CA		

A method of sterilizing objects as well as the sterilized objects obtained from the method are disclosed. The method involves contacting an object such as a medical device to be reused with polycationic dendrimer under conditions which result in rendering a conformationally altered protein (e.g. a prion) non-infectious. A disinfecting agent or surgical scrub composition which comprises the dendrimers is also disclosed as are gelatin capsules treated with polycationic dendrimers.

10 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

L3: Entry 12 of 21 File: USPT Feb 11, 2003

DOCUMENT-IDENTIFIER: US 6517855 B2
TITLE: Method of sterilizing

Detailed Description Text (74):
Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible. (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions. (2) Treatment of PrP 27-30 with acid decreases turbidity and increases a-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

☐ 13. Document ID: US 6514747 B2

L3: Entry 13 of 21 File: USPT Feb 4, 2003

US-PAT-NO: 6514747
DOCUMENT-IDENTIFIER: US 6514747 B2

NAME	CITY	STATE	ZIP CODE	COUNTRY
Woychik; Richard P.	Orinda	CA		
Bultman; Scott J.	Lakewood	OH		
Michaud; Edward J.	Kingston	TN		

US-CL-CURRENT: 435/252.3; 435/254.11, 435/320.1, 435/325, 536/23.1, 536/23.5, 536/24.33

ABSTRACT:

Disclosed are methods and compositions comprising novel agouti polypeptides and the polynucleotides which encode them. Also disclosed are DNA segments encoding these proteins derived from human and murine cell lines, and the use of these polynucleotides and polypeptides in a variety of diagnostic and therapeutic applications. Methods, compositions, kits, and devices are also provided for identifying compounds which are inhibitors of agouti activity, and for altering fatty acid synthetase activity and intracellular calcium levels in transformed cells.

51 Claims, 83 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 41

L3: Entry 13 of 21 File: USPT Feb 4, 2003

DOCUMENT-IDENTIFIER: US 6514747 B2
TITLE: Agouti polynucleotide compositions and methods of use

Detailed Description Text (662):
Appl. Publ. No. WO 87/00880. Intl. Pat. Appl. Publ. No. WO 88/10315. Intl. Pat. Appl. Publ. No. WO 89/06700. Intl. Pat. Appl. Publ. No. WO 90/14424. Intl. Pat. Appl. Publ. No. WO 90/1443. Intl. Pat. Appl. Publ. No. WO 91/03162. Intl. Pat. Appl. Publ. No. WO 92/07065. Intl. Pat. Appl. Publ. No. WO 93/23569. Intl. Pat. Appl. Publ. No. WO 93/15187. Intl. Pat. Appl. Publ. No. WO 93/23569. Intl. Pat. Appl. Pubi. No. WO 94/02595. Intl. Pat. Appl. Publ. No. WO 94/13688. Intl. Pat. Appl. Pubi. No. WO 94/13688. Intl. Pat. Appl. Publ. No. WO 94/02595. Intl. Pat. Appl. Publ. No. WO 96/05309. Intl. Pat. Appl. Publ. No. WO 97/00319. Intl. Pat. Appl. Publ. No. WO 97/11192. Intl. Pat. Appl. Publ. No. WO 97/26335. Intl. Pat. Appl. Publ. No. WO 97/40280. Intl. Pat. Appl. Publ. No. GB 2,202,328. Intl. Pat. Appl. Publ. No. PCT/US89/01025. Abel and Zemel, Am. J. Hypertens., 6:500-504, 1993. Adelman et al., DNA, 2/3:183-193, 1983. Ahmad, Finkelstein, Downs, Frohman, "Obesity-associated decrease in growth hormone-releasing hormone gene expression: a mechanism for reduced growth hormone mRNA levels in genetically obese Zucker rats," Neuroendocrinol., 58:332-337, 1993. Ahmad, Steggles, Carrillo, Finkelstein, "Obesity-and sex-related alterations in growth hormone messenger RNA levels," Mol. Cell. Endocrinol., 65:103-109, 1989. Algate and McCubrey, "Autocrine transformation of hemopoietic cells resulting from cytokine message stabilization aker intracisternal A particle transposition," Oncogene, 8:1221-1232, 1993. Allen and Choun, "Large unilamellar liposomes with low uptake into the reticuloendothelial system," FEBS Lett., 223:42-46, 1987. Altschul, Gish, Miller, Myers, Lipman, "Basic local alignment search tool," J. Mol. Biol., 215:403-410, 1990. Angeggi et al., J.

Ausubel, Brent, Kingston, Moore, Seidman, Smith, Struhl, In: Current Protocols Molecular Biology, Wiley, N.Y., 1988. Aviv and Leder, "Purification of biologically active globin messenger RNA by chromatography on oligothymidylic acid-cellulose," Proc. Natl. Acad. Sci., 69:1408-1412, 1972. Baichwal and Sugden, "Vectors for gene transfer derived from animal DNA viruses: Transient and stable expression of transferred genes," In: Kucherlapati R, ed. Gene transfer. New York: Plenum Press, pp. 117-148, 1986. Balazsovits et al., "Analysis of the effect of liposome encapsulation on the vesicant properties, acute and cardiac toxicities, and antitumor efficacy of doxorubicin," Cancer Chemother. Pharmacol., 23:81-86, 1989. Balling, Mutter, Gruss, Kessel, Cell, 58:337-347, 1989. Barcellini-Couget, Vassaux, Negrel, Ailhaud, "Rise in cytosolic Ca.sup.2+ abolishes in preadipose cells the expression of lipoprotein lipase stimulated by growth hormone," Biochem. Biophys. Res. Commun., 199:136-143, 1994. Barsh and Epstein, "Physical and genetic characterization of a 75-kilobase deletion associated with a/, a recessive lethal allele at the mouse agouti locus," Genetics, 121:811-818, 1989a. Barsh and Epstein, "The long-range restriction map surrounding the mouse agouti locus reveals a disparity between physical and genetic distances," Genomics, 5:9-18, 1989b. Bates and Swift, Gene, 26:137-146, 1983. Bayer and Wilchek, "The use of the avidin-biotin complex as a tool for molecular biology," In: Methods of Biochemical Analysis, Glick, D., John Wiley and Sons, New York, 1980. Beam, Knudson, J. Gen. Physiol, 91:781-798, 1988. Beer, Jakubowicz, Beer, Arocha, Nestler, "Disparate effects of insulin reduction with diltiasem on serum dehydroeiandrosterone sulfate levels in obese hypertensive men and women," J. Clin. Endocrinol. Metab., 79:1077-1081, 1994. Beer, Jakubowicz, Beer, Arocha, Nestlet, "Effects of nitrendipine on glucose tolerance and serum insulin and dehydroepiandrosterone sulfate levels in insulin-resistant obese and hypertensive men," J. Clin. Endocrinol. Metab., 76:178-183, 1993. Begum, Sussman, Draznin, "Calcium-induced inhibition ofphophoserine phosphatmse in insulin target cells is mediated by the phosphorylation and activation of inhibitor 1," J. Biol. Chem., 267:5959-5963, 1992. Begum, Sussman, Draznin, "High levels of cytosolic free calcium inhibit dephosphorylation of insulin receptor and glycogen synthase," Cell Calcium, 12:423-430, 1991. Benvenisty and Neshif, "Direction introduction of genes into rats and expression of the genes," Proc. Nat. Acad. Sci. USA, 83:9551-9555, 1986. Biedler et al., J. Immunol., 141:4053, 1988. Blake and Clarke, "Suppression of rat hepatic fatty acid synthase and S14 gene transcription by dietary polyunsaturated fat," J. Nutr., 120:1727-1729, 1990. Blanchard, Harris, Ittoop, Nichols, Parks, Truesdale, Wilkison, Biochem., 34:10406-10411,1995. Blatt, Abetdam Schwartz, Sachs, "DNA rearrangement of a homeobox gene in myeloid leukaemic cells," EMBO J., 7:4283-4290, 1988. Bolivar et al., Gene, 2:95, 1977. Bollag, Roth, Beaudoir, Mochly-Rosen, Koshland, Jr., "Protein kinase C directly phosphorylates the insulin receptor in vitro and reduces its protein kinase activity," Proc. Natl. Acad. Sci. USA, 83:5822-5824, 1987. Bonadonna and Defronzo, In: Obesity, (Bjorntorp and Brodoff, eds., Lippincott, Philadelphia, pp. 474-502, 1992. Boston and Cone, "Characterization of melanocortin receptor subtype expression in murine adipose tissues and in the 3T3-L1 cell line," Endocrinol., 137:2043-2050, 1996. Bradford, "A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding," Anal. Biochem., 72:248-254, 1976. Bradley, Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, (ed. Robinson, E. J.) 113-151, IRL, Oxford, 1987. Bray and York, "Hypothalamic and genetic obesity in experimental animals: an autonomic and endocrine hypothesis," Physiol. Rev., 59:719-809, 1979. Bray, "Mechanisms for development of genetic, hypothalamic and dietary obesity," In: Pennington Center Nutrition Series (Bray and Ryan, eds), 1st ed., Vol. 5, Molecular and Genetic Aspects of Obesity, Louisiana State University Press, Baton Rouge, La., pp. 3-66, 1996.

membrane with an alkaline buffer," In: Current Protocols in Molecular Biology, Boston, John Wiley and Sons, Ausubel et al. Eds., Vol. 1, p. 297, 1993. Buffey, Edfeeombe MaeNeil, "Calcium plays a complex role in the regulation of melanogenesis in murine B16 melanoma cells, Pigm. Cell Res., 6:385-393, 1993. Bultman, Klebig, Michaud, Sweet, Davisson, Woychik, "Molecular analysis of reverse mutations from nonagouti (a) to black-and-tan (a.sup.t) and white-bellied agouti (A.sup.w) reveals alternative forms of agouti transcripts," Genes Dev., 8:481-490, 1994. Bultman, Michaud, Woychik, "Molecular charecterization of the mouse agouti locus," Cell, Bultman, Russell, Gutierrez-Espeleta, Woychik, "Molecular characterization of a region of DNA associated with mutations at the agouti locus in the mouse," Proc. Natl. Acad Sci. USA, 88:8062-8066, 1991. Byers and Steiner, Annu. Rev. Med, 43:269-289, 1992. Byyny, LoVerde, Mithchell, Draznin, "Cytosolic calcium and insulin resistance in elderly patients," Am. J. Hypertension, 5:459-464, 1992. Cabilly et al., Proc. Natl. Acad. Sci. USA, 84:3439, 1987. Calarco and Pederson, "Ultrastructural observations of lethal yellow (A.sup.y /A.sup.y) mouse embryos, J. Embryol. Exp. Morphol., 35:73-80, 1976. Calvo, Vila-Jato, Alonso, "Effect of lysozyme on the stability of polyester nanocapsules and nanoparticles: stabilization approaches," Biomaterials, 18(19):1305-1310, 1997. Calvo, Vila-Jato, Alonso, "Improved ocular bioavailability of indomethacin by novel ocular drug carriers," J. Pharm. Pharmacol., 48(11):1147-1152, 1996. Campbell et al., Meth. Immunol., Wash. Benjamin, Inc., 1964. Campbell, "Monoclonal Antibody Technology, Laboratory Techniques in Biochemistry and Molecular Biology," Vol. 13, Burden and Von Knippenberg, Eds. pp. 75-83, Elsevier, Amsterdam, 1984. Capecchi, "High efficiency transformation by direct microinjection of DNA into cultured mammalian cells," Cell 22(2):479488, 1980. Carpenter and Mayer, "Physiologic observations on yellow obesity in the mouse," Am. J. Physiol., 193:499-504, 1958. Carteret al., Biochim. Biophys. Acta, 951(1):130-138, 1988. Castle and Little, "On a modified Mendelian ratio among yellow mice," Science, 32:868-870, 1910. Chakrabarty and Leveille, "Acetyl CoA carboxylase and fatty acid synthetase activities in liver and adipose tissue of meal-fed rats," Proc. Soc. Exp. Biol. Med., 131:1051-1054, 1969. Changet al., Nature, 375:615, 1978. Chee et al., Science, 274(5287):610-614, 1996. Chen and Okayama, "High-efficiency transformation of mammalian cells by plasmid DNA," Mol. Cell. Biol., 7:2745-2752, 1987. Chen et al., Nucl. Acids Res., 20:4581-9, 1992. Chen, Charlat, Tartaglia, Woolf, Weng, Ellis, Lakey, Culpepper, Moore, Breitbart, Duyk, Tepper, Morgenstern, Cell, 84:491-495, 1996. Chhajlani and Wikberg, FEBS Lett., 309:417-420, 1992. Chhajlani, Muceniece, Wikberg, Biochem. Biophys. Res. Commun., 195:866-873, 1993. Chou and Fasman, "Conformational Parameters for Amino Acides in Helical, .beta.-Sheet, and Random Coil Regions. Calculated from Proteins," Biochemistry, 13(2):211-222, 1974b. Chou and Fasman, "Empirical Predictions of Protein Conformation," Ann. Rev. Biochem., 47:251-276, 1978b. Chou and Fasman, "Prediction of .beta.-Turns," Biophys. J., 26:367-384, 1979. Chou and Fasman, "Prediction of Protein Conformation," Biochemistry,

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☐ 14. Document ID: US 6451541 B1

L3: Entry 14 of 21 File: USPT Sep 17, 2002

US-PAT-NO: 6451541
DOCUMENT-IDENTIFIER: US 6451541 B1

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Winnacker; Ernst-Ludwig	80638 Munchen			DE
Weiss; Stefan	80799 Munchen			DE
Edenhofer; Frank	80339 Munchen			DE
Rieger; Roman	82362 Weilheim			DE

US-CL-CURRENT: 435/7.1; 424/130.1, 424/139.1, 424/185.1, 424/192.1, 435/70.1, 435/70.2, 435/71.1, 436/501, 436/503, 436/518, 436/528, 436/547, 530/350, 530/387.1

ABSTRACT:

The present invention relates to methods for the detection or isolation of prion proteins by use of chaperones specifically binding to said proteins. The invention further relates to a method for in vitro diagnosis of a transmissible spongiform encephalopathy and to pharmaceutical compositions, preferably for the prevention or treatment of said disease.

18 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 4

L3: Entry 14 of 21 File: USPT Sep 17, 2002

DOCUMENT-IDENTIFIER: US 6451541 B1
TITLE: Chaperones capable of binding to prion proteins and distinguishing the isoforms PrPc and PrPsc

Detailed Description Text (34):
CITED REFERENCES 1. Altmann, H., W. Wendler and E.-L. Winnacker. Transcriptional activation by CTF proteins is mediated by a bipartite low-proline domain. Proc. Natl. Acad. Sci. USA. 91 (1994), 3901-3905. 2. Aiken, J. M., J. L. Williamson and R. F. Marsh. Evidence for Mitochondrial Involvement in Scrapie Infection. J. Virol. 63 (1989), 1686-1694. 3. Alper, T., D. A. Haig and M. C. Clarke. The exceptionally small size of the scrapie agent. Biochem. Biophys. Res. Commun. 22 (1966), 278-284. 4. Alper, T., W. A. Cramp, D. A. Haig and M. C. Clarke. Does the agent of scrapie replicate without nucleic acid? Nature 214 (1967), 764-766. 5. Basler, K., B. Oesch, M. Scott, D. Westaway, M. Walchli, D. F. Groth, M. P. McKinley, S. B. Prusiner and C. Weissmann. Scrapie and cellular PrP isoforms are encoded by the same chromosomal gene. Cell 46 (1986), 417-428. 6. Benson, J. D. and P. M. Howley. Amino-Terminal Domains of the Bovine Papillomavirus Type 1 E1 and E2 Proteins Paticipate in Complex Formation. J. Virol. 69 (1995), 4364-4372. 7. Bessen, R. A., D. A. Kocisko, G. J. Raymond, S. Nandan, P. T. Lansbury and B. Caughey. Non-genetic propagation of strain-specific properties of scrapie prion protein. Nature 375 (1995),698-700. 8. Borchelt, D. R., A. Taraboulos and S. B. Prusiner. Evidence for synthesis of scrapie prion proteins in the endocytic pathway. J. Biol. Chem. 267 (1992), 16188-16199. 9. Borchelt, D. R., M. Scott, A. Taraboulos, N. Stahl and S. B. Prusiner. Scrapie and cellular prion proteins differ in their kinetics of synthesis and topology in cultured cells. J. Cell Biol. 110 (1990), 743-752. 10.

Liebman. Role of the Chaperone Protein Hsp104 in Propagation of the Yeast Prion-Like Factor [psi.sup.+]. Science 268 (1995), 880-884. 13. Ellis J. Proteins as molecular chaperones. Nature 328 (1987), 378-379. 14. Fenton, W. A., Y. Kashi, K. Furtak and A. L. Horwich. Residues in chaperonin GroEL required for polypeptide binding and release. Nature 371 (1994), 614-619. 15. Fields, S. and K.-O. Song. A novel genetic system to detect proteinprotein interactions. Nature 340 (1989), 245-246. 16. Ganea, E. and J. J. Harding. Molecular chaperones protect against glycation-induced inactivation of glucose-6-phosphate dehydrogenase. Eur. J. Biochem. 231 (1995) 181-185. 17. Gasset, M., M. A. Baldwin, R. J. Fietterick and S. B. Prusiner. Perturbation of the secondary structure of the scrapie prion protein under conditions that alter infectivity. Proc. Natl. Acad. Sci. USA. 90 (1993), 1-5. 18. Gething, M.-J. and J. Sambrook. Protein folding in the cell. Nature 355 (1992), 33-45. 19. Golemis, E. A., J. Gyuris and R. Brent. Interaction Trap/Two-Hybrid System to identify interacting proteins. in Current Protocols in Mol. Biol., (Ausubel etal. ed.) (1994) pp 13.14.1-13.14.17, Wiley & Sons. 20. Groschup, M. H., J. Langeveld and E. Pfaff. The major species specific epitope in prion proteins of ruminants. Arch. Virol. 136 (1994), 423-431. 21. Gyuris, J., E. Golemis, H. Chertkov and R. Brent. Cdi1, a Human G1 and S Phase Protein Phosphatase That Associates with Cdk2. Cell 75 (1993), 791-803. 22. Hartl, F. U. and J. Martin. Molecular chaperones in cellular protein folding. Curr. Opinion Struct. Biol. 5 (1995), 92-102. 23. Hartl, F. U., J. Martin and W. Neupert. Protein Folding in the Cell: The Role of Molecular Chaperones Hsp70 and Hsp60. Ann. Rev. Biophys. Biomol. Sruct. 21 (1992), 293-322. 24. Huang, Z., J.-M. Gabriel, M. A. Baldwin, R. J. Fletterick, S. B. Prusiner and F. E. Cohen. Proposed three-dimensional structure for the cellular prion protein. Proc. Natl. Acad. Sci. USA. 91 (1994), 7139-7143. 25. Itoh, H., R. Kobayashi, H. Wakui, A. Komatsuda, H. Ohtani, A. B. Miura, M. Otaka, O. Masamune, H. Andoh, K. Koyama, Y. Sato and Y. Tashima. Mammalian 60-kDa Stress Protein (Chaperonin Homolog). Identification, Biochemical Properties and Localization. J. Biol. Chem. 270 (1995), 13429-13435. 26. Kazmirski, S. L., D. O. V. Alonso, F. E. Cohen, S. B. Prusiner and V. Daggett. Theoretical studies of sequence effects on the conformational properties of a fragment of the prion protein: implications for scrapie formation. Chemistry & Biology 2 (1995), 305-315. 27. Kocisko, D. A., S. A. Priola, G. J. Raymond, B. Chesebro, P. T. Jr. Lansbury and B. Caughey. Species specifity in the cell-free conversion of prion protein to protease-resistant forms: A model for the scrapie species barrier. Proc. Natl. Acad. Sci. USA. 92 (1995), 3923-3927. 28. Kocisko, D. A., J. H. Come, S. A. Priola, B. Chesebro, G. J. Raymond, P. T. Lansbury and B. Caughey. Cell-free formation of protease-resistent prion protein. Nature 370 (1994), 471-474. 29. Lansbury, P. T. Jr. and B. Caughey. The chemistry of scrapie infection: implications of the `ice 9` metaphor. Chemistry & Biology 2 (1995), 1-5. 30. Nguyen, J., M. A. Baldwin, F. E. Cohen and S. B. Prusiner. Prion Protein Peptides Induce .alpha.-helix to .beta.-sheet Conformational Transitions. Biochemistry 34 (1995), 4186-4192. 31. Pan, K.-M., M. Baldwin, J. Nguyen, M. Gasset, A. Serban, D. Groth, I. Mehlhorn, Z. Huang, R. J. Fletterick, F. E. Cohen and S. B. Prusiner. Conversion of .alpha.-helices into .beta.-sheets features in the formation of the scrapie prion proteins. Proc. Natl. Acad. Sci. USA 90 (1993), 10962-10966. 32. Phadtare, S., M. T. Fisher and L. R. Yarbrough. Refolding and release of tubulins by a functional immobilized groEL column. Biochim. et Biophys. Acta 1208 (1994), 189-192. 33. Prusiner, S. B. and K. K. Hsiao. Human prion diseases. Ann. Neurol. 35 (1994), 385-395. 34. Prusiner, S. B. Molecular biology of prion disease. Science 252 (1991), 1515-1522. 35. Prusiner, S. B., D. F. Groth, D. C. Bolton, S. B. Kent and L. E. Hood. Purification and structural studies of a major scrapie prion protein. Cell 38 (1984), 127-134. 36. Prusiner, S. B. Novel proteinaceous infectious particles cause Scrapie. Science 216

Higuchi, G. T. Horn, K. B. Mullis and Erlich, H. A. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. Science 239 (1988), 487-491. 40. Sambrook J., E. F. Fritsch and T. Maniatis. Molecular Cloning. A Laboratory Manual, 2nd ed. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. 41. Sanger, F., S. Nicklen and A. R. Coulson. DNA sequencing with chain terminating inhibitors. Proc. Natl. Acad. Sci. USA 74 (1977), 5463-5467. 42. Stahl, N., M. A. Baldwin, D. B. Teplow, L. Hood, B. W. Gibson, A. L. Burlingame and S. B. Prusiner. Structural studies of the scrapie prion protein using mass spectrometry and amino acid sequencing. Biochemistry 32 (1993), 1991-2002. 43. Telling, G. C., M. Scott, J. Mastrianni, R. Gabizon, M. Torchia, F. E. Cohen, S. J. DeArmond and S. B. Prusiner. Prion Propagation in Mice Expressing Human and Chimeric PrP Transgenes Implicates the Interaction of Cellular PrP with Another Protein. Cell 83 (1995), 79-90. 44. Towbin, H., T. Staehelin and J. Gordon. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. Proc. Natl. Acad. Sci. USA 76 (1979), 4350-4354. 45. Velez-Granell, C. S., A. E. Arias, J. A. Torres-Ruiz and M. Bendayan. Molecular chaperones in pancreatic tissue: the presence of cpn10, cpn60 and hsp70 in distinct compartments along the secretory pathway of the acinar cells. J. Cell. Sci. 107 (1994), 539-549. 46. Vitek, M. P., K. Bhattacharya, J. M. Glendening, E. Stopa, H. Viassara, R. Bucala, K. Manogue and A. Cerami. Advanced glycation end products contribute to amyloidosis in Aizheimer disease. Proc. Natl. Acad. Sci. USA. 91 (1995), 4766-4770. 47.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 15. **Document ID: US 6419916 B1**

L3: Entry 15 of 21 File: USPT Jul 16, 2002

US-PAT-NO: 6419916

DOCUMENT-IDENTIFIER: US 6419916 B1

TITLE: Assay for compounds which affect conformationally altered proteins

DATE-ISSUED: July 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Prusiner; Stanley B.	San Francisco	CA		
Supattapone; Surachai	San Francisco	CA		
Scott; Michael R.	San Francisco	CA		

US-CL-CURRENT: 424/78.32; 424/78.35, 424/78.36, 424/78.37, 424/78.38, 424/DIG.16

ABSTRACT:

An assay comprises contacting cells containing a conformationally altered protein with test compound and determining if the altered protein is cleared. The cells may be scrapie-infected neuroblastoma cells. Another assay comprises contacting organ

8 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

L3: Entry 15 of 21 File: USPT Jul 16, 2002

DOCUMENT-IDENTIFIER: US 6419916 B1
TITLE: Assay for compounds which affect conformationally altered proteins

Detailed Description Text (63):
Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible. (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions. (2) Treatment of PrP 27-30 with acid decreases turbidity and increases a-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

Full | Title | Citation | Front | Review | Classification | Date | Reference | | | Claims | KWIC | Draw De

☐ 16. Document ID: US 6368813 B1

L3: Entry 16 of 21 File: USPT Apr 9, 2002

US-PAT-NO: 6368813
DOCUMENT-IDENTIFIER: US 6368813 B1

TITLE: Multiflavor streptavidin

DATE-ISSUED: April 9, 2002

INVENTOR-INFORMATION:

Cantor; Charles Del Mar CA

US-CL-CURRENT: 435/7.5; 435/69.1, 435/7.1, 530/300, 530/350, 536/23.1, 536/23.7

ABSTRACT:

Compounds and methods are described for producing streptavidin mutants with changed affinities. In particular, modifications to the sequence of the natural streptavidin gene is described to create amino acid substitutions resulting in greater affinity for biotin substitutes than for biotin.

21 Claims, 0 Drawing figures
Exemplary Claim Number: 1

L3: Entry 16 of 21 File: USPT Apr 9, 2002

DOCUMENT-IDENTIFIER: US 6368813 B1
TITLE: Multiflavor streptavidin

Detailed Description Text (52):
where the last term DEw accounts for changes in the self-energy of water. Each of the terms in EQ 3 is a sum over energies of all atoms in the complex, with each term accounting for electrostatic and van der Waals energies. The first two terms in EQ 3 can be neglected because the conformational energy change of both streptavidin and biotin is very small upon formation of the complex. Another simplification that reduces computational work is the fact that protein-ligand and protein-solvent interfaces are well-packed to the extent that changes in the van der Waals component of DEs-1 and DE1-w and DEs-w are very small, so that it is only necessary to consider electrostatic forces for these terms [Adamson, in Physical Chemistry of Surfaces, Wiley, N.Y. (1976); Novotny et al., "On the attribution of binding energy in antigen-antibody complexes McPC603, D1.3, and HyHEL-5," Biochem. 28:4735-4749 (1989)]. To calculate the Gibbs free energy (EQ 4) it is necessary to calculate the entropic contribution, namely T(Sb-Sf), where T is temperature and S, entropy, and the subscripts refer to streptavidin with and without biotin.

☐ 17. Document ID: US 6331296 B1

L3: Entry 17 of 21 File: USPT Dec 18, 2001

US-PAT-NO: 6331296
DOCUMENT-IDENTIFIER: US 6331296 B1

TITLE: Food additives which affect conformationally altered proteins

DATE-ISSUED: December 18, 2001

Scott; Michael R. San Francisco CA 94114

US-CL-CURRENT: 424/78.08; 424/405, 424/438, 424/439, 424/442, 424/78.17, 424/78.18, 424/78.27, 424/78.31, 424/78.32, 424/78.33, 424/78.34, 424/78.35, 426/271, 426/532, 523/122, 525/512, 525/513, 525/514

ABSTRACT:

An assay comprises contacting cells containing a conformationally altered protein with test compound and determining if the altered protein is cleared. The cells may be scrapie-infected neuroblastoma cells. Another assay comprises contacting organ or tissue homogenate (at pH 5.0 or less) with test compound to determine if altered protein in the homogenate is cleared. The homogenate may be brain homogenate from a transgenic mouse infected with human prions. Compounds which are found to clear the altered protein are useful in preventing, arresting and/or reversing (i.e. treating) a disease associated with the conformationally altered protein.

11 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

L3: Entry 17 of 21 File: USPT Dec 18, 2001

DOCUMENT-IDENTIFIER: US 6331296 B1
TITLE: Food additives which affect conformationally altered proteins

Detailed Description Text (110):
Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible. (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions. (2) Treatment of PrP 27-30 with acid decreases turbidity and increases a-helical content, suggesting that such conditions might dissociate PrP.sup.Sc into monomers (Safar, J., Roller, P. P., Gajdusek, D. C. & Gibbs, C. J., Jr. Scrapie amyloid (prion) protein has the conformational characteristics of an aggregated molten globule folding intermediate). It is therefore possible that polyamines bind to an equilibrium unfolding intermediate of PrP.sup.Sc present under acidic conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

US-PAT-NO: 6322802
DOCUMENT-IDENTIFIER: US 6322802 B1
**** See image for Certificate of Correction ****

TITLE: Method of sterilizing

DATE-ISSUED: November 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Prusiner; Stanley B.	San Francisco	CA		
Supattapone; Surachai	San Francisco	CA		
Scott; Michael R.	San Francisco	CA		

US-CL-CURRENT: 424/405; 128/114.1, 128/832, 128/899, 422/27, 424/78.08, 424/78.18, 424/78.27, 424/78.35, 424/DIG.16, 528/363, 600/29, 600/3, 600/30, 600/36, 600/372, 604/890.1, 623/1.1, 623/920

ABSTRACT:

A method of sterilizing objects as well as the sterilized objects obtained from the method are disclosed. The method involves contacting an object such as a medical device to be reused with polycationic dendrimer under conditions which result in rendering a conformationally altered protein (e.g. a prion) non-infectious. A disinfecting agent or surgical scrub composition which comprises the dendrimers is also disclosed as are gelatin capsules treated with polycationic dendrimers.

6 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

L3: Entry 18 of 21 File: USPT Nov 27, 2001

DOCUMENT-IDENTIFIER: US 6322802 B1
**** See image for Certificate of Correction ****
TITLE: Method of sterilizing

Detailed Description Text (100):
Without committing to any particular mechanism of action it appears likely that branched polyamines require the acidic environment of intact endosomes or lyzosomes to destroy PrP.sup.Sc. The structure-activity profile of polymers tested reveals that the most active compounds possess densely packed, regularly-spaced amino groups, suggesting that these compounds may bind to a ligand which has periodically-spaced negative charges. Several scenarios remain possible. (1) Branched polyamines may bind directly to PrP.sup.Sc arranged as an amyloid with exposed negatively-charged moieties and induce a conformational change under acidic conditions. (2) Treatment of PrP 27-30 with acid decreases turbidity and increases

conditions. (3) Alternatively, polyamines might sequester a cryptic, negatively charged component bound to PrP.sup.Sc that is essential for protease resistance, but which is only released when PrP.sup.Sc undergoes an acid-induced conformational change. Such a component might act as a chaperone for PrP.sup.Sc inside endosomes or lysosomes. (4) Finally, another possibility is that polyamines activate an endosomal or lysosomal factor which can induce a conformational change in PrP.sup.Sc. Clearly, more work will be required to determine the precise mechanism by which branched polyamines destroy PrP.sup.Sc.

☐ 19. Document ID: US 6226603 B1

L3: Entry 19 of 21 File: USPT May 1, 2001

US-PAT-NO: 6226603
DOCUMENT-IDENTIFIER: US 6226603 B1

TITLE: Method for the prediction of binding targets and the design of ligands

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Freire; Ernesto	Baltimore	MD		
Luque; Irene	Baltimore	MD		

US-CL-CURRENT: 703/11; 702/19, 702/27, 703/12

ABSTRACT:

A computer-based method for the identification of binding targets in proteins and other macromolecules. More particularly, the invention includes an algorithm aimed at predicting binding targets in proteins. This algorithm, named Woolford, requires knowledge of the high resolution structure of the protein but no knowledge of the location or identity of natural binding sites or ligands. Binding targets in the protein are identified and classified according to their expected optimal affinities. Binding targets can be located at the protein surface or at internal surfaces that become exposed as a result of partial unfolding, conformational changes, subunit dissociation, or other events. The entire protein is mapped according to the binding potential of its constituent atoms. Once binding targets are identified, optimal ligands are designed and progressively built by the addition of individual atoms that complement structurally and energetically the selected target.

7 Claims, 25 Drawing figures
Exemplary Claim Number: 2
Number of Drawing Sheets: 25

L3: Entry 19 of 21 File: USPT May 1, 2001

Detailed Description Text (42):
The Gibbs energy of binding is composed of enthalpic and entropic components. Both components include contributions due to the formation of interactions between ligand and protein, and contributions due to changes in hydration. The enthalpic contributions are a function of the separation distance between atoms and the changes in atomic accessibility to the solvent. The entropy change contain solvent contributions which are also proportional to changes in solvent accessibility, and the reduction in conformational degrees of freedom. Changes in translational degrees of freedom are the same for different ligands and therefore do not contribute to discrimination between binding affinities even though they contribute to the actual affinity.

Detailed Description Text (62):
In the above situation, the total Gibbs energy associated with the binding of the ligand is the sum of the Gibbs energy required to unfold the region of the protein that exposes the binding site (or the Gibbs energy for the conformation change) plus the intrinsic Gibbs energy of binding.

Detailed Description Text (97):
The Gibbs energy of binding is composed of enthalpic and entropic components. Both components include contributions due to the formation of interactions between ligand and protein, and contributions due to changes in hydration. The enthalpic contributions are a function of the separation distance between atoms and the changes in atomic accessibility to the solvent. The entropy change contains solvent contributions which are also proportional to changes in solvent accessibility, and the reduction in conformational degrees of freedom. Electrostatic interactions and protonation/deprotonation events coupled to binding are also important and are included in the analysis. Changes in translational degrees of freedom are the same for different ligands and therefore do not contribute to discriminate between binding affinities even though they contribute to the actual affinity.

Detailed Description Text (105):
In all cases presented here the Gibbs energy of binding, .DELTA.G, was calculated from the published crystallographic structures using procedures previously described (D'Aquino et al., 1996; Gomez et al., 1995(a); Gomez et al., 1995(b); Hilser et al., 1996(b); Luque et al., 1996). These calculations require the structures of the complex as well as the structures of the unligated protein and unligated inhibitor. In this approach, the generic portion of the Gibbs energy, .DELTA.G.sub.gen, is calculated from a separate computation of its enthalpy and entropy components. This portion of the Gibbs energy contains those contributions typically associated with the formation of secondary and tertiary structure (van der Waals interactions, hydrogen bonding, hydration and conformational entropy). Additional contributions to the Gibbs energy of binding are not separated into enthalpic and entropic components. They include electrostatic and ionization effects, Gion, and the contribution of the change in translational degrees of freedom, .DELTA.G.sub.tr,

Detailed Description Text (147):
FIG. 11 shows the predicted and experimental binding affinities for the thirteen HIV-1 protease inhibitors considered here. For those protease/inhibitor complexes for which the structure of the free enzyme is available the calculations were performed by using both, the structure of the free enzyme (Spinelli et al., 1991), as well as the structure of the enzyme in the complex but without the inhibitor, as

inhibitor. The statistical analysis of the data reveals that the free energies of binding are predicted with a standard deviation of .+-.1.1 kcal/mol and a standard error of 0.3 kcal/mol. The standard deviation amounts to a relative uncertainty of .+-.10%. The correlation analysis between the experimental and predicted .DELTA.G values yields a slope of 0.982 with a correlation coefficient of 0.85. The structural predictions show no systematic deviations and are accurate enough to permit an examination of the different contributions to the binding energetics.

Detailed Description Text (169):
Once the mutation is made it is necessary to sample the ensemble of possible conformations and evaluate the energy and corresponding probability of each conformation. The probability of a single peptide conformation, defined by a specific set of side chain and backbone coordinates, is dictated by a Gibbs energy function, .DELTA.G.sub.ef, specified by the enthalpy of intra and intermolecular peptide/protein interactions plus the enthalpy and entropy of solvation. .DELTA.G.sub.ef is a function of the side chain and backbone torsional angles. By definition, the conformational entropy of the peptide itself does not enter into the equation. .DELTA.G.sub.ef is the Gibbs energy function or Gibbs potential function of a single conformation and should not be confused with the Gibbs energy of binding which includes all permissible conformations. The situation is illustrated in FIGS. 15A and 15B for two hypothetical conformations of a side chain. These conformations exhibit not only different intramolecular interactions but also different degrees of solvation that define the Gibbs energy function, .DELTA.G.sub.ef. The probability of any given conformation is given by the equation ##EQU4##

Detailed Description Text (178):
The binding affinity of the peptide for the protein is dictated by the Gibbs energy of binding which is calculated from the structures of the complex, the free protein and the free peptide as described before (Bardi et al., 1997; D'Aquino et al., 1996; Gomez et al., 1995(a); Gomez et al., 1995(b); Hilser et al., 1996(b); Luque et al., 1996). For each mutant complex the atomic coordinates corresponding to the conformation that minimizes the Gibbs potential function were used. For the free peptides the solvent accessibilities correspond to a Boltzmann weighted average of side chain and backbone conformations (Luque et al., 1996).

Detailed Description Text (184):
For endothiapepsin, the high resolution structures of the protein in its free and bound forms are known, and accurate calculations of binding affinities are possible. In many cases, however, only the structure of the complex is known. If this is the case, the binding Gibbs energies of the mutants relative to the wild type can still be calculated with the same accuracy, and therefore peptide design can be done with the same precision. This situation holds even if there is a significant conformational change between the free and complexed proteins.

Detailed Description Text (188):
In the case of the E7 mutant, the length of the peptide has been increased at the carboxy terminus. The additional glutamate is pointing outward from the body of the protein and does not interact significantly with any residue. This is reflected in the similar enthalpies and heat capacities observed for this mutant and the wild type pepstatin A. The difference in binding Gibbs energies is mainly entropic and due primarily to the loss of conformational entropy of the glutamate upon binding. This loss of conformational entropy is not compensated by a favorable interaction either enthalpic or entropic, and results in a significant [illegible] .DELTA.G [illegible]

☐ 20. Document ID: US 6114113 A

L3: Entry 20 of 21 File: USPT Sep 5, 2000

US-PAT-NO: 6114113
DOCUMENT-IDENTIFIER: US 6114113 A

TITLE: High efficiency genetic modification method

DATE-ISSUED: September 5, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
McLaughlin-Taylor; Elizabeth	San Clemente	CA		
Kruger; Mark	Encinitas	CA		
Lundak; Cheryl	San Diego	CA		
Killion; Catherine	Long Beach	CA		

US-CL-CURRENT: 435/5; 435/372.3, 435/440, 435/455, 435/456

ABSTRACT:

A method is provided for producing a population of genetically modified T cells. In the method, an in vitro population of T cells is activated by contacting said population with a CD3 binding agent. Genetic modification is then carried out with the activated T cells by contacting the same with a suitable gene transfer vector.

50 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

L3: Entry 20 of 21 File: USPT Sep 5, 2000

DOCUMENT-IDENTIFIER: US 6114113 A
TITLE: High efficiency genetic modification method

Detailed Description Text (48):
The normal protein C anticoagulant pathway requires activation by the enzyme thrombin. Thrombin is normally a procoagulant enzyme which cleaves fibrinogen to form fibrin, activates platelets, and performs positive feedback reactions on components of the coagulation cascade. Thrombin activity in the anticoagulant pathway under physiological conditions is dependent upon binding to an endothelial cell surface-bound cofactor, thrombomodulin. Upon binding to this protein, thrombin undergoes a conformational change that greatly reduces it's ability to perform the procoagulant reactions mentioned above, while greatly increasing the rate of activation of protein C zymogen, thus changing specificity from a procoagulant to an anticoagulant enzyme. In accordance with this model, infusion of low levels of

of these variants by the means of gene transfer vectors and the methods of genetic modification described herein is thus useful in reducing thrombosis in individuals at risk thereof.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 21. Document ID: US 5230998 A

L3: Entry 21 of 21 File: USPT Jul 27, 1993

US-PAT-NO: 5230998
DOCUMENT-IDENTIFIER: US 5230998 A

TITLE: Method for the prescreening of drugs targeted to the V3 hypervariable loop of the HIV-1 envelope glycoprotein gp 120

DATE-ISSUED: July 27, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Neurath; Alexander R.	New York	NY	10021	
Strick; Nathan	Oceanside	NY	11572	
Haberfield; Paul	Brooklyn	NY	11204	
Jiang; Shibo	New York	NY	10025	

US-CL-CURRENT: 435/7.1; 435/7.72, 435/7.9, 435/7.92, 435/7.94, 435/7.95, 435/974, 436/532

ABSTRACT:

A method for the rapid screening of a drug targeted to the V3 hypervariable loop of the human immunodeficiency virus type 1 or type 2 envelope glycoprotein gp 120 comprising measuring the inhibitory effect of the drug on the interaction between gp 120 (or an antigen comprising the V3 hypervariable loop of HIV 1 gp 120 or HIV 2 gp 120) and antibodies specific for the V3 hypervariable loop, and anti-HIV chemotherapy with drugs binding to the V3 hypervariable loop.

7 Claims, 19 Drawing figures
Exemplary Claim Number: 7
Number of Drawing Sheets: 13

L3: Entry 21 of 21 File: USPT Jul 27, 1993

DOCUMENT-IDENTIFIER: US 5230998 A
TITLE: Method for the prescreening of drugs targeted to the V3 hypervariable loop of the HIV-1 envelope glycoprotein gp 120

C., Meloen, R. H., Smit, L., Bakker, M., Asher, D. M., Wolff, A. V., Gibbs Jr., C. J., and Gajdusek, D. C. (1988), "Human Immunodeficiency Type 1 Neutralization Epitope with Conserved Architecture Elicits Early Type-specific Antibodies in Experimentally Infected Chimpanzees", Proc. Natl. Acad. Sci. USA, 85, 4478-4482; Goudsmit, J., Kuiken, C. L., and Nara, P. L. (1989), "Linear Versus Conformational Variation of V3 Neutralization Domains of HIV-1 During Experimental and Natural Infection", AIDS, 3, S119-S123; Linsley, P. S., Ledbetter, J. A. , Kinney-Thomas, E., and Hu, S. L. (1988), "Effects of Anti-gp120 Monoclonal Antibodies on CD4 Receptor Binding by the env Protein of Human Immunodeficiency Virus Type 1", J. Virol., 62, 3695-3702; Matsushita, S., Robert-Guroff, M., Rusche, J., Koito A., Hattori, T., Hoshino, H., Javaherian, K., Takatsuki, K., and Putney, S. D. (1988), "Characterization of a Human Immunodeficiency Virus Neutralizing Monoclonal Antibody and Mapping of the Neutralizing Epitope", J. Virol., 62, 2107-2114; Palker, T. J., Clark, M. E., Langlois, A. J., Matthews, T. J., Weinhold, K. J., Randall, R. R., Bolognesi, D. P. and Haynes, B. F. (1988), "Type-Specific Neutralization of the Human Immunodeficiency Virus with Antibodies to env-encoded Synthetic Peptides", Proc. Natl. Acad. Sci. USA, 85, 1932-1936; Rusche, J. R., Javaherian, K., McDanal, C., Petro, J., Lynn, D. L., Grimaila, R., Langlois, A., Galo, R. C., Arthur, L. O., Fischinger, P. J., Bolognesi, D. P., Putney, S. D. and Matthews, T. J. (1988), "Antibodies that Inhibit Fusion of Human Immunodeficiency Virus-infected Cells Bind a 24-amino Acid Sequence of the Viral Envelope, gp120", Proc. Natl. Acad. Sci. USA, 85, 3198-3202; Skinner, M. A., Langlois, A. J., McDanal, C. B., McDougal, J. S., Bolognesi, D. P., and Matthews, T. J. (1988), "Neutralizing Antibodies to an Immunodominant Envelope Sequence do not Prevent gp120 Binding to CD4", J. Virol., 62, 4195-4200; Kenealy, W. R., Matthews, T. J., Ganfield, M. C., Langlois, A. J., Waselefsky, D. M., and Petteway, Jr. S. R. (1989), "Antibodies from Human Immunodeficiency Virus-infected Individuals Bind to a Short Amino Acid Sequence that Elicits Neutralizing Antibodies in Animals," AIDS Res. Human Retroviruses, 5, 173-182; Javaherian, K., Langlois, A. J., McDanal, C., Ross, K. L., Eckler, L. I., Jellis, C. L., Profy, A. T., Rusche, J. R., Bolognesi, D. P., Putney, S. D., and Matthews, T. J. (1989), "Principal Neutralizing Domain of the Human Immunodeficiency Virus type 1 Envelope Protein, Proc. Natl. Acad. Sci. USA, 86, 6768-6772; Javaherian, K., Langlois, A. J., LaRosa, G. J., Profy, A. T., Bolognesi, D. P., Herlihy, W. C., Putney, S. C., Matthews, T. J. (1990), "Broadly Neutralizing Antibodies Elicited by the Hypervariable Neutralizing Determinant of HIV-1", Science, 250, 1590-1593; Fung, M. S. C., Sun, C. R. Y., Liou, R. S., Gordon, W.; Chang, N. T., Chang, T. W., and Sun, N. C. (1990), "Monoclonal Anti-idiotypic Antibody Mimicking the Principal Neutralization Site in HIV-1 gp120 Induces HIV-1 Neutralizing Antibodies in Rabbits" J. Immunol., 145, 2199-2206; Hart, M. K., Palker, T. J. Matthews, T. J., Langlois, A. J., Lerche N. W., Martin, M. E. Scearce, R. M., McDanal, C., Bolognesi, D. P., and Haynes, B. F. (1990), "Synthetic Peptides Containing T and B Cell Epitopes From Human Immunodeficiency Virus Envelope gp120 Induce anti-HIV Proliferative Responses and High Titers of Neutralizing Antibodies in Rhesus Monkeys., J. Immunol., 145, 2677-2685; Neurath et al, (1990), J. Gen. Virol., 71, 85-95; Profy, A. T., Salinas, P. A., Eckler, L. I., Dunlop, N. M., Nara, P. L., and Putney, S. C., (1990), "Epitopes Recognized by the Neutralizing Antibodies of an HIV-1-infected Individual", J. Immunol., 144, 4641-4647 and Scott, Jr., C. F., Silver, S., Profy, A. T., Putney, S. D., Langlois A., Weinhold, K., and Robinson, J. E. (1990), "Human Monoclonal Antibody that Recognizes the V3 Region of Human Immunodeficiency Virus gp120 and Neutralizes the Human T-Lymphotropic Virus type III.sub.MN Strain," Proc. Natl. Acad. Sci. USA. 87, 8597-8601.

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